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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,899	09/27/2001	Dalia Cohen	4-31612A/USN	3252

1095 7590 01/29/2004

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,899	COHEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *4-26 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 27-30* is/are rejected.

7)☒ Claim(s) *1 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *None* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II, claims 1-3 and 27-30 in the election received 11/26/2003 is acknowledged. The traversal is on the ground(s) that a transgenic fly comprising a nucleotide encoding Abeta40 (Invention I) and a transgenic fly comprising a nucleotide encoding Abeta42 (Invention II) are related as combination and subcombination. This is not found persuasive because the similarity in sequence between the nucleotides encoding Abeta40 and Abeta42 are not grounds for relating the inventions as combination subcombination. Applicant argues that The DNA sequences of SEQ ID NO:1 and 2 differ by only 6 contiguous nucleotides (see election, page 6, lines 3-6). While the fly comprising a transgene encoding Abeta42 comprises the same nucleotide sequences that encode Abeta40, it does not produce Abeta40 from the Abeta42 encoding transgene. Therefore, the fly comprising the Abeta42 transgene is not a subcombination of the fly comprising the transgene encoding Abeta40. It is clear from the teachings of the specification that Abeta40 and Abeta42 have different roles in Alzheimer's disease and that the ratio of Abeta40 to Abeta42 is important (page 2, lines 15-26 and page 3, lines 1-3). Therefore, the flies comprising a transgene encoding each of these polypeptides are distinct and unobvious one over the other. A transgene encoding Abeta40 would have a different effect on a fly than that encoding Abeta42. The requirement is still deemed proper and is therefore made FINAL.

Claims 4-26 and 31-109 and claims 1-3 and 27-30 as they relate to Abeta42 (SEQ ID NO:1), are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to

a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the election received 11/26/2003.

Claim Objections

Claims 1 and 27 step (a) is objected to because of the following informalities: Claim 1 and claim 27, step (a) are grammatically incorrect. The last phrase "and expressing said DNA sequence..." does not fit grammatically with the rest of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 27-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic fly comprising a DNA sequence encoding Abeta42 operably linked to an eye-specific expression control sequence wherein expression of said DNA sequence results in said fly displaying a rough eye phenotype and a method of using said fly to identify compounds that treat or ameliorate neural degeneration or symptoms of Alzheimer's Disease, does not reasonably provide enablement for said fly wherein the DNA sequence encoding Abeta42 is operably linked to any tissue-specific expression control sequence wherein expression of said DNA sequence results in said fly displaying any phenotype or a method of using said fly to identify compounds that affect any condition or prevent any

condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are drawn to a transgenic fly whose genome comprises a DNA sequence encoding Abeta42 fused to a signal sequence and operably linked to a tissue specific expression control sequence wherein said DNA sequence results in said fly displaying an altered phenotype. Claim 2 limits the specific expression control sequence to the GMR promoter. Claim 3 limits the altered phenotype to a "rough-eye" phenotype. Claims 27-30 are drawn to methods of using the claimed fly to identify compounds useful for treatment, prevention or amelioration of conditions associated with abnormal regulation of the APP pathway.

The specification teaches generating transgenic Drosophila using a GMR-Abeta42 transgene, which comprises DNA encoding the Abeta42 peptide operably linked to the eye-specific Glass Multimer Reporter (GMR) promoter (page 46, lines 8-19). Flies exhibited a dosage dependent effect of the transgene wherein higher copy numbers resulted in a more extreme rough eye phenotype (page 46, line 21-page 47, line 13). Increased levels of Abeta42 cause a rough eye phenotype as a result of a disrupted arrangement of photoreceptor cells in the eye (page 46, lines 21-30). Originally, 2 independent transgenic lines were generated (K18.1 and K18.3) with K18.3 demonstrating a greater effect on the phenotype of the fly (page 46, lines 25-27). Low levels o expression of Abeta42 in lines K18.1 and K18.3 caused changes in the structure of the eye that were not detectable macroscopically (page 49, line 25-page 50, line 2). Due to the position effect causing variations in transgene expression, 19 additional transgenic lines were constructed to generate flies with great levels of transgene expression (page 47, lines

18-30). Line KJ103 was determined to have a greater level of phenotypic severity (page 48, lines 8-16) as a result of a greater level of Abeta42 production (page 49, lines 21-23). The specification teaches that the phenotype resulting from expression of the Abeta42 transgene worsens with age, mimicking the progressive worsening f Alzheimer's disease symptoms (page 52, lines 4-5).

The breadth of the claims encompasses a transgenic fly comprising an Abeta42 transgene operably linked to any tissue specific expression control sequence wherein expression of the transgene results in any altered phenotype. The specification teaches generating transgenic Drosophila using a GMR-Abeta42 transgene, which comprises DNA encoding the Abeta42 peptide operably linked to the eye-specific Glass Multimer Reporter (GMR) promoter (page 46, lines 8-19) wherein increased levels of Abeta42 peptide result in a rough eye phenotype. The specification does not teach overexpression of Abeta42 in any tissue other than the eye and does not teach any phenotype other than the rough eye phenotype.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). Kellum taught that the expression level of transgenes in

flies is also susceptible to position effects (Cell, 1991, Vol. 64, pages 941-950). This phenomenon is supported in the specification as the independent lines of Abeta42 transgenic flies express different levels of Abeta42 from the transgene (page 47, lines 18-20; page 46, lines 21-30). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 273-276). With regard to the importance of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4). Thus, the phenotype caused by a particular gene of interest is dependent upon the tissue specificity of the promoter used to express the transgene.

1) The specification fails to enable using any tissue-specific expression control sequence other than an eye-specific expression control sequence (claims 1 and 27). Claims 3 and 27 encompass a transgenic fly overexpressing Abeta42 in non-eye and non-neural tissues. The specification teaches using the GMR vector, which directs expression in the eye. The specification does not teach overexpression of Abeta42 in any tissue other than the eye. Based on the state of the art described above, the phenotype caused by overexpression of Abeta42 in any tissue other than the eye is unpredictable. The specification does not offer the guidance necessary to cause a phenotype equivalent to the rough eye phenotype in any non-eye tissue and fails to provide any teachings as to what the effect of overexpression of Abeta42 in any fly tissue other

than the eye would be. One of skill in the art would not know how to use a fly overexpressing Abeta42 in a non-eye tissue.

2) The specification further fails to enable making and using a transgenic fly overexpressing Abeta42 wherein the fly exhibits any altered phenotype (claims 1,2,27,28 and 29). The specification teaches how to make and use a fly exhibiting a rough eye phenotype. The specification does not teach how to make or use a fly with any phenotype other than a rough eye phenotype. One of skill in the art would not know how to use a transgenic fly exhibiting a phenotype other than rough eye. Furthermore, based on the unpredictability of phenotype as set forth by state of art described above, it would require undue experimentation for one of skill in the art to determine how to make the claimed fly such that it exhibits any altered phenotype other than the rough eye phenotype.

3) The specification fails to enable identifying compounds useful for treatment, prevention or amelioration of any condition associated with abnormal regulation of the APP pathway as encompassed by claim 27. The claim encompasses any condition associated with abnormal regulation of APP, however, the specification teaches only neurodegeneration of the photoreceptor cells leading to the rough eye phenotype. The art at the time of filing demonstrated that increased levels of Abeta42 can lead to amyloid deposition, synaptic abnormalities and gliosis, for example (Siman, 2000, Journal of Neuroscience, Vol. 20, pages 8717-8726, specifically, abstract, column 2, lines 8-9 and page 8717, column 1, 1st paragraph). The specification does not teach any phenotype other than neurodegeneration that is associated with abnormal regulation of the APP pathway. Therefore one of skill in the art would not know how to carry out the method of claim 27 wherein the condition is any condition associated with

abnormal regulation of APP pathway other than neurodegeneration because one of skill in the art would not know how to generate the claimed fly having any phenotype other than neurodegeneration in the eye.

4) The breadth of claims 27-30 includes methods of identifying compounds for prevention of a condition, which encompasses treatment of a subject wherein the subject does not exhibit a disease state to prevent the onset of the disease state. The specification is not enabling for identifying a compound that prevents a condition. Prevention or prophylaxis requires that the disease state be stopped before it has begun. The specification does not teach how to assess whether a subject will acquire a rough eye or other neurodegenerative phenotype prior to the subject exhibiting symptoms. Once a subject exhibits a phenotype, the methods encompassed by the claims would meet the qualifications for treatment, but not prevention. There are no teachings or guidance in the specification with regard to which subjects would be at risk for developing a phenotype such that the phenotype can be inhibited prior to its onset or at what stage the claimed methods would be carried out to prevent onset of the phenotype.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632